



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2026-N-2642]

Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List Additions and Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; established list additions and request for comments.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is adding constituents to the list of harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke (the established HPHC list) as required by the Federal Food, Drug, and Cosmetic Act (the FD&C Act).

DATES: Either electronic or written comments on the notice must be submitted by **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov> Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your

comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2026-N-2642 for "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List Additions and Request for Comments." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include

the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Anna Julia Adams or Matthew Brenner, Center for Tobacco Products, Food and Drug Administration, Document Control Center, Bldg. 71, Rm. G335, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002; 1-877-287-1373, CTPRegulations@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Introduction

The Family Smoking Prevention and Tobacco Control Act (Pub. L. 111-31), enacted on June 22, 2009, amended the FD&C Act by, among other things, adding a new chapter (chapter

IX) granting FDA the authority to regulate the manufacture, marketing, and distribution of tobacco products to protect the public health. Cigarettes, cigarette tobacco, roll-your-own (RYO) tobacco, and smokeless tobacco were immediately subject to chapter IX.

For other types of tobacco products, the statute authorizes FDA to issue regulations “deeming” them to be subject to chapter IX. FDA published a final rule on May 10, 2016, deeming all products that meet the statutory definition of “tobacco product” set forth in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)), including components and parts, but excluding accessories of deemed products, to be subject to chapter IX of the FD&C Act.¹

Section 904(e) of the FD&C Act (21 U.S.C. 387d(e)) requires FDA to establish, and periodically revise as appropriate, “a list of harmful and potentially harmful constituents, including smoke constituents, to health in each tobacco product by brand and by quantity in each brand and subbrand.”

In 2011, FDA provided guidance that discussed the meaning of “harmful and potentially harmful constituent” in the context of the HPHC list requirement (76 FR 5387, January 31, 2011).² In 2012, after considering comments solicited from the public, as well as scientific and other information, FDA developed a list of 93 constituents in tobacco products and tobacco smoke that are believed to be harmful or potentially harmful to health (the HPHC established list).³

In August 2016, FDA extended its authority under the Deeming Rule to all products, including components and parts (but excluding accessories of deemed products) that met the

¹ See “Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act,” 81 FR 28974 (May 10, 2016), codified at 21 CFR part 1100. On August 9, 2023, the U.S. District Court for the District of Columbia issued an order vacating FDA’s rule deeming tobacco products to be subject to FDA’s tobacco product authorities “insofar as it applies to premium cigars.” *Cigar Ass’n of Am. v. FDA*, No. 16-cv-01460, 2023 WL 5094869, at *6 (D.D.C. Aug. 9, 2023), affirmed in part, reversed in part, and remanded, 132 F.4th 535 (D.C. Cir. 2025).

² FDA revised the 2011 Guidance that discusses the meaning of HPHC in the context of the HPHC list requirement in August 2016. “Harmful and Potentially Harmful Constituents” in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act available at <https://www.fda.gov/media/80109/download>.

³ “Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List,” 77 FR 20034 (April 3, 2012).

statutory definition of tobacco product, including electronic nicotine delivery systems (ENDS). Therefore, consistent with section 904(e) of the FD&C Act, the Agency considered revising the HPHC established list to reflect the current range of tobacco products now subject to the Agency's tobacco product authorities as well as the Agency's growing scientific expertise with respect to all tobacco products. In 2019, the Agency requested comments on whether 19 additional constituents should be added to the HPHC established list. The Agency has considered comments solicited from the public, as well as scientific and other information, and has added tobacco product constituents to the established HPHC list that FDA currently believes are harmful or potentially harmful to health based on scientific evidence. FDA is adding 18 new constituents to the established list consistent with the requirement in section 904(e) of the FD&C Act to periodically revise, as appropriate, the established HPHC list (Table 1). In this document, we are also finalizing the addition of a new criterion for whether a constituent should be added to the list and seeking comments on the proposed addition of three new constituents to the list.

II. Background

FDA first established the HPHC list on April 3, 2012 (77 FR 20034) (the April 2012 notice).⁴ The list currently contains 93 HPHCs. The April 2012 notice describes the history of the HPHC established list, and for additional background, we refer readers to that notice and the notice FDA published in the *Federal Register* on August 12, 2011 (76 FR 50226) (the August 2011 notice), in which we solicited public comment, including scientific and other information, concerning the HPHCs in tobacco products and tobacco smoke, such as constituents that should be included on the HPHC established list, and the criteria used in determining whether a constituent is harmful or potentially harmful such that it should be included on the HPHC list.⁵

Further, on August 5, 2019 (84 FR 38032) (the August 2019 notice), FDA published a

⁴ "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List," 77 FR 20034 (April 3, 2012).

⁵ "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments," 76 FR 50226 (August 12, 2011).

request for comments on 19 additional constituents proposed to be added to the established list to reflect the current range of tobacco products subject to the Agency's tobacco product authorities as well as the Agency's growing scientific expertise with respect to all tobacco products. The August 2019 notice mentions FDA's application of existing criteria to deemed tobacco products to propose the addition of glycidol and ethylene glycol. Glycidol is a thermal byproduct of glycerol and a common component in e-liquids. Ethylene glycol, which has also been identified in e-liquids, adversely affects reproduction and development. The notice also stated that FDA would tentatively apply one additional criterion regarding whether a constituent should be included on the HPHC list: constituents identified by the National Institute for Occupational Safety and Health (NIOSH) as having adverse respiratory effects. The notice also proposed diethylene glycol (DEG) be added to the list due to it being a potential contaminant in either glycerol or propylene glycol. If ingested, DEG can cause kidney failure, neurological damage, and death.

When determining whether a constituent should be included on the established HPHC list, FDA considers whether there is evidence that the constituent meets established criteria, such as determinations from third-party scientific and public health organizations like NIOSH, the Environmental Protection Agency (EPA) or the Agency for Toxic Substances and Disease Registry (ATSDR). As part of the Centers for Disease Control and Prevention, NIOSH is the Federal agency responsible for conducting research and making science-based recommendations to prevent work-related illness and injuries, including those related to human health hazards and respiratory disease from inhalation exposures to toxicants. FDA has now finalized its previously tentative conclusion that constituents identified by NIOSH as respiratory toxicants will be an additional criterion that will be applied for determining whether a constituent should be included on the HPHC established list. The previously established criteria for determining whether a constituent should be included on the established HPHC list includes constituents identified by the EPA or ATSDR as having adverse respiratory or cardiac effects. Considering information

from NIOSH in this regard is consistent with FDA’s current practice of looking to other recognized, government experts such as EPA or ATSDR for their ability to identify constituents as having adverse respiratory or cardiac effects. As indicated by the original criteria (the April 2012 notice), FDA has previously considered this information from NIOSH when determining whether a constituent is harmful or potentially harmful by including constituents identified by NIOSH as a potential occupational carcinogen as a current criterion.

After review and consideration of the relevant comments received from the August 2019 notice, FDA is adding 18 of the 19 proposed constituents to the HPHC list. Although FDA proposed that ethyl acetoacetate be added to the list, based on it having been tentatively identified as a respiratory toxicant, FDA has determined that there is insufficient information to warrant its inclusion on the list at this time. FDA’s determination is based on the fact that ethyl acetoacetate does not meet any of the criteria for adding constituents to the HPHC list, including that NIOSH has not identified it as having adverse respiratory effects. This determination may be revised, consistent with the directive in section 904(e) of the FD&C Act that FDA periodically revise the established list as appropriate. The list of the constituents added to the established HPHC list is in Table 1.⁶

Table 1.--List of the Additional Chemicals and Chemical Compounds Identified by FDA as Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke

Constituent	Carcinogen (CA), Respiratory Toxicant (RT), Reproductive or Developmental Toxicant (RDT), Poisonous Chemical (PC)
Acetic Acid	RT
Acetoin (also known as 3-hydroxy-2-butanone)	RT
Acetyl Propionyl (also known as 2,3-pentanedione)	RT
Benzyl Acetate	RT
Butyraldehyde	RT
Diacetyl	RT
Diethylene Glycol	PC
Ethyl Acetate	RT
Ethylene Glycol	RT, RDT
Furfural	RT
Glycerol	RT
Glycidol	CA
Isoamyl Acetate	RT
Isobutyl Acetate	RT
Methyl Acetate	RT

⁶ See Appendix A for complete HPHC established list.

n-Butanol	RT
Propionic Acid	RT
Propylene Glycol	RT

III. Request for Comments and Information

Based on the August 2019 notice, FDA received several comments that suggested adding constituents to the established HPHC list beyond those proposed in the notice. FDA has statutory authority under section 904(e) of the FD&C Act and intends to continue to revise the established HPHC list as additional criteria are defined and additional scientific information becomes available. As a result of comments to the August 2019 notice, FDA is proposing to add three additional constituents to the established list and requests comments on the three proposed additions: pulegone, furfuryl alcohol, and methyl eugenol. These constituents are often added to e-liquid formulations as flavors, but may also be present in other tobacco products, such as cigarettes and smokeless tobacco. FDA has tentatively concluded that these three constituents meet the criteria used in determining whether a constituent is harmful or potentially harmful and should be included on the HPHC established list, unless other scientific information obtained by or submitted to the Agency shows that the constituent is not, in fact, harmful or potentially harmful.

IV. Identification of HPHCs is an Ongoing Effort

FDA continues to review relevant science to determine whether to add additional constituents to the list. That a constituent has not been so identified by FDA or other entities could be because it does not currently meet established criteria, it has not been adequately studied, or it has not yet been systematically reviewed. Consistent with the obligations under section 904(e) of the FD&C Act, FDA intends to continue: (1) our efforts to review other disease outcomes to assess whether additional chemicals or chemical compounds in tobacco products or tobacco smoke, including chemicals or chemical compounds in the emissions from the range of tobacco products now deemed to be subject to chapter IX of the FD&C Act, are harmful or

potentially harmful constituents that contribute to the risk of other diseases; (2) our consideration of whether additional or different criteria should be selected to help identify other classes of harmful or potentially harmful chemicals and chemical compounds for inclusion on the HPHC established list and whether individual constituents should be added; and (3) our efforts to review new information to determine if it would be appropriate to remove one or more of the constituents that appear on the HPHC established list, or to add additional constituents to the list.

Appendix A --Established List of the Chemicals and Chemical Compounds Identified by FDA as Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke

Constituent	Carcinogen (CA), Respiratory Toxicant (RT), Cardiovascular Toxicant (CT), Reproductive or Developmental Toxicant (RDT), Addictive (AD), Poisonous Chemical (PC), Banned in Food (in Smokeless Tobacco Products)
Acetaldehyde	CA, RT, AD
Acetamide	CA
Acetic Acid	RT
Acetoin (also known as 3-hydroxy-2-butanone)	RT
Acetone	RT
Acetyl Propionyl (also known as 2,3-pentanedione)	RT
Acrolein	RT, CT
Acrylamide	CA
Acrylonitrile	CA, RT
Aflatoxin B1	CA
4-Aminobiphenyl	CA
1-Aminonaphthalene	CA
2-Aminonaphthalene	CA
Ammonia	RT
Anabasine	AD
o-Anisidine	CA
Arsenic	CA, CT, RDT

A- α -C (2-Amino-9H-pyrido[2,3-b]indole)	CA
Benz[a]anthracene	CA, CT
Benz[j]aceanthrylene	CA
Benzene	CA, CT, RDT
Benzo[b]fluoranthene	CA, CT
Benzo[k]fluoranthene	CA, CT
Benzo[b]furan	CA
Benzo[a]pyrene	CA
Benzo[c]phenanthrene	CA
Benzyl Acetate	RT
Beryllium	CA
1,3-Butadiene	CA, RT, RDT
Butyraldehyde	RT
Cadmium	CA, RT, RDT
Caffeic acid	CA
Carbon monoxide	RDT
Catechol	CA
Chlorinated dioxins/furans	CA, RDT
Chromium	CA, RT, RDT
Chrysene	CA, CT
Cobalt	CA, CT
Coumarin	Banned in food
Cresols (o-, m-, and p-cresol)	CA, RT
Crotonaldehyde	CA
Cyclopenta[c,d]pyrene	CA
Diacetyl	RT
Dibenz[a,h]anthracene	CA
Dibenzo[a,c]pyrene	CA
Dibenzo[a,h]pyrene	CA

Dibenzo[<u>a,i</u>]pyrene	CA
Dibenzo[<u>a,l</u>]pyrene	CA
Diethylene Glycol	PC
2,6-Dimethylaniline	CA
Ethyl Acetate	RT
Ethyl carbamate (urethane)	CA, RDT
Ethylbenzene	CA
Ethylene Glycol	RT, RDT
Ethylene oxide	CA, RT, RDT
Formaldehyde	CA, RT
Furan	CA
Furfural	RT
Glu-P-1 (2-Amino-6-methyl-dipyrido[1,2- <u>a</u> :3',2'- <u>d</u>]imidazole)	CA
Glu-P-2 (2-Aminodipyrido[1,2- <u>a</u> :3',2'- <u>d</u>]imidazole)	CA
Glycerol	RT
Glycidol	CA
Hydrazine	CA, RT
Hydrogen cyanide	RT, CT
Indeno[1,2,3- <u>cd</u>]pyrene	CA
IQ (2-Amino-3-methylimidazo[4,5- <u>f</u>]quinoline)	CA
Isoamyl Acetate	RT
Isobutyl Acetate	RT
Isoprene	CA
Lead	CA, CT, RDT
MeA- α -C (2-Amino-3-methyl)-9H-pyrido[2,3- <u>b</u>]indole)	CA
Mercury	CA, RDT
Methyl Acetate	RT

Methyl Ethyl Ketone	RT
5-Methylchrysene	CA
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	CA
Naphthalene	CA, RT
n-Butanol	RT
Nickel	CA, RT
Nicotine	RDT, AD
Nitrobenzene	CA, RT, RDT
Nitromethane	CA
2-Nitropropane	CA
<u>N</u> -Nitrosodiethanolamine (NDELA)	CA
<u>N</u> -Nitrosodiethylamine	CA
<u>N</u> -Nitrosodimethylamine (NDMA)	CA
<u>N</u> -Nitrosomethylethylamine	CA
<u>N</u> -Nitrosomorpholine (NMOR)	CA
<u>N</u> -Nitrosornicotine (NNN)	CA
<u>N</u> -Nitrosopiperidine (NPIP)	CA
<u>N</u> -Nitrosopyrrolidine (NPYR)	CA
<u>N</u> -Nitrososarcosine (NSAR)	CA
Normicotine	AD
Phenol	RT, CT
PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5- <u>b</u>]pyridine)	CA
Polonium-210	CA
Propionic Acid	RT
Propionaldehyde	RT, CT
Propylene Glycol	RT
Propylene oxide	CA, RT
Quinoline	CA
Selenium	RT

Styrene	CA
o-Toluidine	CA
Toluene	RT, RDT
Trp-P-1 (3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole)	CA
Trp-P-2 (1-Methyl-3-amino-5H-pyrido[4,3-b]indole)	CA
Uranium-235	CA, RT
Uranium-238	CA, RT
Vinyl acetate	CA, RT
Vinyl chloride	CA

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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